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February 17, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: Docket No. 2004N-0479, Draft Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals

Dear Sir or Madam:

The American Veterinary Medical Association, on behalf of its 71,000 members, provides the following comments on Docket Number 2004N-0479, Draft Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals.

The AVMA is the national professional association of veterinarians whose members are charged ethically and legally with the protection of the health of animals within their care, as well as the protection of public health. The overarching objective of the AVMA is to advance the science and art of veterinary medicine, including its relationship to public health, biological science, and agriculture. In furtherance of that objective, we submit these comments.

Risk Assessment
Executive Summary
The draft risk assessment states,

> *"It is difficult to assess the extent of transfer of streptogramin resistance from virginiamycin-exposed E. faecium to E. faecium found in human infections based on the available data. Literature reports demonstrate that there are differences in the characteristics of resistant E. faecium isolated from animal and human sources, with respect to minimum inhibitory concentration (MIC) distributions and the presence of known resistance genes. These two findings, along with the current incomplete knowledge of the genetic basis of streptogramin resistance, prevents the risk assessment from making firm conclusions as to* ***whether****, and, if so,* ***how much****, the use of streptogramins in food animals contributes to the occurrence of streptogramin-resistant E. faecium infections in humans via a foodborne pathway."*
> [Emphasis added]

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Given the findings summarized in the preceding statement, we do not understand why the Food and Drug Administration proceeded to publish the subject speculative risk assessment.

The assumed, estimated food pathway attribution factor of 10% in the draft risk assessment is derived from the studies of Willems et al. on vancomycin-resistant *E. faecium* (VRE) isolates in Europe. However, the epidemiology of VRE is very different in Europe and the U.S. and the low rate of community carriage of VRE in the U.S. compared to Europe suggests that a food pathway attribution factor of 10% is an inappropriately high estimate.

Further, we are concerned that an unfounded, assumed food pathway attribution factor of 100% was chosen to model an alternative theoretical scenario. The food pathway attribution factor of 100% has no basis. The risk assessment states (Page 94), "[FDA] CVM was also interested in risk estimates given an assumption that *all* existing resistance to streptogramins among the human population originated in food animal uses of virginiamycin. [Emphasis is the in the draft risk assessment] This statement seems to indicate that CVM does not limit itself to evidence-based assumptions and, instead, seeks to dramaticize the results of this risk assessment by artificially inflating the results. Because of the known differences in the characteristics of resistant *E. faecium* isolated from animal and human sources, if the Agency decides to proceed with a 100% modeling scenario, another counter scenario should include an assumed food pathway attribution factor of 0%.

Risk Assessment
Introduction
The bacterium that is the subject of this risk assessment is *Enterococcus faecium*, not all *Enterococcus* species. Therefore, the discussion of nosocomial enterococcal infections in the first paragraph of the Introduction needs to be limited to nosocomial *E. faecium* infections, not all enterococcal infections.

Risk Assessment
Introduction
The Concern for Transfer of Streptogramin Resistance
The risk assessment provides examples of what might occur but provides little evidence of what does occur. For example, the risk assessment states, "Clinical antimicrobial resistance as a result of opportunistic infection is possible from two different pathways: first, animal-derived, resistant *E. faecium* might colonize the human coincidently with streptogramin resistance; and, second, animal–derived *E. faecium* might transfer resistance genes to the human *E. faecium* prior to or coincidently with antimicrobial treatment". On this point, the Australian Pesticides and Veterinary Medicines Authority states, in *Findings of the Reconsideration of the Registration of Products Containing Virginiamycin, and Their Labels*, November 2004, "Colonization of humans by animal-derived *E. faecium* and/or transfer of resistance to human strains of *E. faecium* may occur, although transfer of resistance has not yet been observed." And, "[C]onclusive evidence of human infection with animal-derived streptogramin-resistant *E. faecium* is lacking". Also, "A recent Danish study examined the effect on volunteers of a virginiamycin-resistant strain of *E. faecium* (six subjects) . . . . (Sorensen et al., 2001). Resistant strains were detected in all subjects until day five after ingestion and in one subject at day 14. The authors concluded that virginiamycin-resistant *E. faecium* can survive gastric passage, multiply, and be isolated for up to 14 days [in 1 of 6 subjects]. . . This study did not demonstrate long-term carriage or gene transmission."

Risk Assessment
2. Hazard Identification
2.3 Identification of the Potential Human Health Impact
2.3.2 Populations at Risk of SREF Infection

The risk assessment states [p. 13], "In fact, a major reason for the risk assessment is that *Enterococcus* species account for as many as 800,000 infections and $500M in medical costs each year." The bacterium that is the subject of this risk assessment is *Enterococcus faecium*, not all *Enterococcus* species. Therefore, the discussion of the impact of enterococcal infections needs to be limited to *E. faecium* infections, not all enterococcal infections. The quoted sentence needs to be deleted.

Risk Assessment
3. Release Assessment
3.3 Prevalence of Resistance in Farm Animals

The risk assessment suggests [p. 40] that unexplained resistance among animals and species with no direct exposure to streptogramins is related to past or continued usage in farm animals. This is highly speculative and unsupported by the studies cited (Butaye, 2001). This statement should be removed.

Risk Assessment
6. Risk Estimation
6.7.1 Sensitivity Analysis

The purpose of a sensitivity analysis is to evaluate the impact of model assumptions and data variability on estimated risks. Analysis of all three models found that community prevalence of Synercid resistance was the dominant variable. The authors use this fact to suggest that additional research is needed to estimate this variable more precisely. However, the purpose of this risk assessment is to determine the impact of animal use of Virginiamycin on human risk of resistant infection and the one variable linking animal and human resistance prevalence--the food attribution fraction--is never addressed or discussed as an influential model assumption or as a significant research gap in this section of the document. The sensitivity results simply confirm that the food attribution fraction is, in fact, the most dominant variable in the model. Better estimates of community prevalence of Synercid-resistant *Enterococcus faecium* may be important, but this is downstream of the most basic assumption upon which the whole model rests: that animal use of Virginiamycin is directly correlated with the community prevalence of Synercid resistance. As the document points out in several places, the strength of this assumption is highly questionable and cannot be left out of the discussion of model sensitivity or research gaps.

We believe that the risk assessment needs to be withdrawn or modified in response to the comments provided in this letter. If republished the risk assessment must be abundantly clear and explicit regarding the numerous assumptions that have been included.

Thank you for the opportunity to comment.

Sincerely,

Bruce W. Little, DVM
Executive Vice President

BWL/SCAR/LPV